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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/632,567	07/31/2003	Paul Workman	CCI-026USRCE	2601

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EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	**PAPER NUMBER**
1618	

MAIL DATE	DELIVERY MODE
01/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/632,567	WORKMAN ET AL.	
	Examiner	Art Unit	
	Melissa Perreira	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,27 and 28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18,27 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/26/07 has been entered.

Priority

It is also acknowledged that applicant asserts that a certified copy of the foreign Great Britain patent application will be filed.

Claims and Previous Rejections Status

2. Claims 1-18,27 and 28 are pending in the application. Claims 22-25 were cancelled and claim 28 newly added in the amendment filed 10/26/07.

3. The rejection of claims 1-18,22-25,27 and 28 under 35 U.S.C. 103(a) as being unpatentable over Dumont et al. (US 6,413,974) in view of the combined teachings of Dumont et al. (US 6,399,633) and Carlson et al. (*Cancer Res.* **1999**, *59,* 4634-4641) is withdrawn. Applicant's assertions are moot in view of the new grounds of rejection.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-18,27 and 28 under 35 U.S.C. 103(a) as being unpatentable over Grant et al. (US 2005/0004007A1) in view of Dumont et al. (US 6,413,974) and further in view of Carlson et al. (*Cancer Res.* **1999**, *59,* 4634-4641).

6. Grant et al. (US 2005/0004007A1) discloses the methods of promoting apoptosis of cancer cells and for treating cancer [i.e. lymphoma, colon cancer (not excluding KM12 colon cancer cells), etc.] in a patient (abstract; p2, [0011]; p4, [0034]) via monitoring the activity of a CDK inhibitor, a combination of CDK inhibitors or a CDK inhibitor/active agent combination (p2, [0011]; p4, [0032]). The CDK inhibitors of the disclosure include flavopiridol, roscovitine, etc. (p2, [0011]). One major function of the cyclin D/CDK 4 complex is to phosphorylate the retinoblastoma protein (pRb) and the inhibition of CDKs results in the pRb dephosphorylation (p1, [0005]; p12, [0091]). It is disclosed that the examination of the administration of the compound flavopiridol alone in cell culture had a minimal effect on pRb dephosphorylation (p8, [0070]) and that the treatment with the compound flavopiridol alone modestly increased ERK activation where activation is defined as MAPK phosphorylation (p9, [0074]). Therefore the increase in ERK (MAPK) phosphorylation is indicative of flavopiridol activity. The doses of flavopiridol after 24 h for clonogenic survival are disclosed in fig 2B. The antibodies

used for the examination of the effects of flavopiridol on phosphorylated pRb and levels of phosphorylated ERK1 and ERK2 are underP-pRb, pRb-CDK2 and pRb-CDK-4 and PhophoPlus p44/p42 MAP Kinase Antibody Kit respectively (p5, [0041]; p6, [0048]). Grant et al. does not teach phosphorylation of Rb at serine 780 or the cell lines of the instant claims.

7. Dumont et al. (US 6,413,974) discloses the co-administration, not excluding a human of more than one cyclin dependent kinase inhibitor (cassette dosing assay) in a therapeutically effective amount (column 42, lines 32-36; column 44, lines 52-54). The cyclin dependent kinase inhibitor roscovitine has been shown to be selective towards some cyclin-dependent kinases where none of the analogs showed superior IC_{50} values over the (R) enantiomer of roscovitine (column 13, lines 28-50). Roscovitine was tested against the human colon adenocarcinoma cell lines HT-29 and HCT-15 (table 1) and in *in vivo* assays where nude mice xenografts where tumor pieces were implanted under the capsule of the kidneys of male nude mice (column 101, lines 5-21).

8. Carlson et al. (*Cancer Res.* **1999**, *59,* 4634-4641) discloses the specific polyclonal antisera that recognizes the phosphorylated serine 780 Rb species to determine the mechanism by which flavopiridol, a cyclin dependent kinase inhibitor, inhibits cyclin D1 abundance in breast carcinoma cells (p 4634, column 2, paragraph 4) thus causing dephosphorylation of pRb. Minimal changes (up to 8 h) were observed in the phosphorylated Rb at serine 780 or in total Rb but Rb phosphorylation declined at 12 h after treatment with flavopiridol (p 4636, paragraph 2).

9. At the time of invention it would have been obvious to one ordinarily skilled in the art to utilize (R)-roscovitine taught by Dumont et al., a selective and a more potent cyclin dependent kinase inhibitor, to monitoring the activity of CDK inhibition or Rb phosphorylation in a cell culture (i.e. HT-29). The increase in ERK (MAPK) phosphorylation is indicative of flavopiridol activity and it would be predictable that roscovitine (also a CDK inhibitor) would increase ERK (MAPK) phosphorylation. The disclosures of Grant et al. and Dumont et al. are drawn to the method of studying the inhibition of CDKs with roscovitine and flavopiridol and therefore it would be obvious to use them interchangeably as flavopiridol has roscovitine-like activity. It would also be obvious to one skilled in the obvious to study the effects of roscovitine and flavopiridol on serine 780 Rb phosphorylation of Rb and levels of phosphorylated ERK1 and ERK2 using the specific antibodies for pRb and ERK1/2 as Carlson et al. discloses the observation of phosphorylation of Rb at serine 780.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melissa Perreira whose telephone number is 571-272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MP
January 3, 2008

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER